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EXAMINER	
NGUYEN, QUANG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,533	WAXMAN ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8-11,13-18,31-33,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8-11,13-18,31-33,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 12/09/09 was entered.

Applicant elected previously the following species: (a) p35 as a species of apoptosis inhibiting agent; (b) cytochrome P450 as a species of a pro-drug activating enzyme; (c)) cyclophosphamide and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase as a species of the prodrug; (d) p53 as a species of a factor promoting apoptosis; and (e) Trail as a species of a death receptor ligand.

Amended claims 1, 3, 8-11, 13-18, 31-33, 37-38 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 102(b) as being anticipated by Melcher et al. (British Journal of Cancer 78:144-145, 1998) was withdrawn in light of Applicant's claim amendments.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1, 3, 8-11, 13-18, 31-33, 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is new ground of rejection necessitated by Applicant's amendment.***

Amended independent claims 1, 11, 13 and 37-38 recite the new limitations "wherein expression of the apoptosis inhibiting agent results in prolonged lifespan of the neoplastic cells thereby increasing expression of the prodrug activating enzyme compared to a life span of a cell not transduced with the vector encoding the apoptosis inhibiting agent", "wherein expression of the nuclei acid encoding an apoptosis inhibiting agent increases the life span of the transduced target neoplastic cell compared to a cell not transduced with an apoptosis inhibiting agent when the mammal is subjected to the prodrug", and "wherein expression of the nucleic acid encoding the apoptosis inhibiting agent increases the life span of the transduced target neoplastic cell in the tumor when the mammal is subjected to the chemotherape4utic drug compared to a life span of a neoplastic cell not transduced with a vector comprising a nucleic acid encoding the apoptosis inhibiting agent". As written, the claims encompass expression of the apoptosis inhibiting agent results in both **a permanent and transient** prolonged lifespan of a neoplastic cell transduced with a vector encoding a recited apoptosis inhibiting agent, particularly a permanent prolonged lifespan of a neoplastic cell even in the presence of a prodrug or a chemotherapeutic drug along with the expression of a heterologous prodrug activating enzyme in said neoplastic cell. The specification as

originally filed does not provide a written support for the methods as now broadly claimed. In the amendment filed on 7/23/09 (page 7, first paragraph), Applicants cited paragraphs 42-51 and 130-132 as alleged supports for the above limitations. However, none of these cited paragraphs provide support for the concept that expression of the apoptosis inhibiting agent results in **a permanent** prolonged lifespan of a neoplastic cell transduced with a vector encoding a recited apoptosis inhibiting agent, even in the presence of a prodrug or a chemotherapeutic drug along with the expression of a heterologous prodrug activating enzyme in said neoplastic cell. On the contrary, at least paragraph 42 stated "We have discovered that delivery of an anti0-apoptotic agent to a cell containing such a therapeutic gene (the "therapeutic factory cell") increases the life span of the cell and increases the net formation by the factory cell of an active chemotherapeutic agent **capable of killing neighboring cells and eventually also the transduced factory cell**"; paragraph 43 stated "We have further discovered that **inhibition of the apoptotoic pathway slows down but ultimately does not prevent the factory cell from dying**"; paragraph 47 stated "For example, **the anti-apoptotic factor p35 when expressed in a P450 factory cell prolongs the life span of the P450 factory cell while allowing the factory cell eventually to die**".

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of invention as now broadly claimed at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 38 recites the limitation "the chemotherapeutic drug" in 12 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because prior to this limitation, only the term "a prodrug" is recited. Therefore, which specific chemotherapeutic drug do Applicants refer to? For the purpose of a compact prosecution, the examiner interprets this limitation to refer to the prodrug.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1, 3, 8-11, 13 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382), Bullock et al. (Exp. Hematol. 21:1640-1647, 1993), Melcher et al. (British Journal of Cancer 78:144-145, 1998) and Beidler et al. (J. Biol. Chem. 270:16526-16528, 1995). ***This is a new ground of rejection necessitated by Applicant's amendment.***

With respect to the elected species, Waxman et al disclose methods of killing neoplastic cells (e.g., melanoma, pancreatic cancer, lung and gastrointestinal cancer, breast cancer, hepatoma) in both *in vitro* and in a mammalian patient, including a human patient, using at least NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes, **wherein the P450 gene and the RED gene are delivered using one or more viral vectors** (e.g., retrovirus, adenovirus, and others), the cytochrome P450 gene is a mammalian gene such as P450 1A1, 1A2, 1B1, 2B1, 2B2, 2B4 and others and the P450-activated chemotherapeutic agent is cyclophosphamide (CPA), ifosfamide (IFA) or any other P450-metabolized chemotherapeutic drug (See at least Summary of the Invention, pages 7-14; page 40, lines 27-30). Waxman et al further teach that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor

necrosis factor alpha, and caspases, and cytokines such as IL-2, IL-4 and IL-12; as well as with other established gene/produrg activation systems such as ganciclovir/HSV-TK (page 12, first full paragraph). Waxman et al also teach targeting specificity for P450 and RED gene delivery is facilitated by "transcriptional targeting" including the use of tumor-specific or tumor-selective DNA enhancer sequences (page 12, second full paragraph; page 31, first full paragraph). Waxman et al also disclose that although the viral genomes of the viral vectors used in the methods should be modified to remove or limit their ability to replicate, however, **replication conditional viruses** are also useful, such as a herpes virus with an inactivated viral ribonucleotide reductase gene that selectively delivered P450 2B1 to tumor cells that overexpress the mammalian ribonucleotide reductase enzyme which is required for this modified virus to replicate (page 33, line 27 continues to line 11 of page 34). Waxman et al also note that **some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression** (page 55, lines 11-13); **tumor cells transfected with both P450/RED genes (e.g., 9L/2B6/reducase cells) are themselves more chemosensitive and more readily killed by CPA and IFA** (see Fig. 15, and page 70, lines 12-13); and **current gene therapy technologies are limited by their inability to deliver prodrug activation or other therapeutic genes to a population of tumor cells with 100% efficiency but the effectiveness of this cancer gene therapy approach can be greatly enhanced by using with drugs exhibiting a strong bystander effect with bystander cytotoxicity resulting when active drug metabolites diffuse or otherwise transferred from their site of generation within a**

transduced tumor cell to a neighboring, naïve tumor cell leads to significant tumor regression even when a minority of tumor cell is tranduced with the prodrug activation gene (page 3, lines 15-28).

Waxman et al do not teach methods of killing neoplastic cells further comprising the step of transducing neoplastic cells containing a vector encoding a prodrug activating enzyme with a vector encoding an apoptosis inhibiting agent, wherein the apoptosis inhibiting agent is selected from the recited Markush group that includes p35 (the elected species).

At the effective filing date of the present application, Bilbao et al already disclosed at least a method **to prolong or enhance transgene expression (up to 2 log increase)**, including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, **due to the attenuation of expression of the transferred therapeutic gene based at least in part due to the cytotoxic effects of the viral products** (see at least the abstract; page 18, line 10 continues to line 3 of page 19; page 19, line 28 continues to line 5 of page 20; examples 26). **Bilbao et al also taught specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach** (page 2, lines 15-27). Bilbao et al further state that **"Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility"** (page 52, lines 6-10).

Additionally, Bullock et al taught that 4-hydroperoxycylco-phosphamide (4-HC), **an active derivative of cyclophosphamide (CPA) induced internucleosomal DNA fragmentation characteristic of apopotosis or programmed cell death as well as significant reduction in bcl-2 in human myeloid leukemia HL60 cells** (see at least the abstract).

Moreover, at the effective filing date of the present application Melcher et al also taught transfecting the CMT93tk line, **the colorectal tumor CMT93 cell line already transfected with HSV thymidine kinase, with a retrovirus encoding bcl2 in an attempt to block apoptotic cell death during HSVtk/GCV killing; and they found that although the transfected cells showed greatly reduced amounts of apoptotic cell death as judged by DNA ladders and propidium iodie staining, the transfected cells were still sensitive to GCV *in vitro*** (see the entire abstract). Melcher et al further proposed **that necrotic cell death in vivo may provide a potent immunostimulatory signal that serves as a "danger" to allow breaking of tolerance to tumor antigens as a result of co-transfecting tumor cells with a vector encoding bcl-2**.

Furthermore, Beidler et al. already taught that **the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery because p35 inhibits at least TNF- and Fas-induced apoptosis** (see at least the abstract; page 16528, col. 1, last paragraph).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. by further comprising at least the step of transducing neoplastic cells

already transduced with both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2 or the baculovirus p35 protein, in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or delayed transiently the death of tumor cells tranduced with both P450/RED genes so to prolong their production and secretion of cytotoxic drug metabolites to neighboring native tumor cells to attain a prolonged bystander cytotoxicity that is known to lead to significant tumor regression, in light of the teachings of Bilbao et al, Bullock et al, Melcher et al and Beidler et al. Please note that Waxman et al already disclosed that **some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression.**

An ordinary skilled artisan would have been motivated to carry out the above modifications **in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or delayed transiently the death of tumor cells tranduced with both P450/RED genes so to prolong their production and secretion of cytotoxic drug metabolites to neighboring native tumor cells to attain a prolonged bystander cytotoxicity that is known to lead to significant tumor regression**. Bilbao et al already demonstrated successfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically state that "Strategies to prolong the expression of transgenes delivered by adenovirus vector,

even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility". Moreover, Melcher et al and Bullock et al already disclosed respectively that **tumor cells even transfected with a recombinant vector encoding bcl-2 were still sensitive to GCV; and that 4-hydroperoxycyclo-phosphamide (4-HC) which is an active derivative of CPA induced internucleosomal DNA fragmentation characteristic of apoptosis and significant reduction of bcl-2 in leukemia cells.** Furthermore, **the baculovirus p35 protein has been demonstrated by Beidler et al to be an inhibitor of the TNF- and Fas-induced apoptosis**.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Bullock et al, Melcher et al. and Beidler et al; coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 7/23/09 (pages 9-12 and 14) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that Melcher reference describes that dual-transduced HSVtk/bcl-2 cells do not die through apoptosis when exposed to GCV, and this teaches

directly away from the present invention which is based upon the surprising discovery that the cells survive longer and are thus are better producers of the pro-drug conversion enzyme upon expression of an apoptosis inducing agent. Without the knowledge of the present application, a skilled artisan could not have envisioned that by adding an apoptosis inhibiting agent to a cell, one can broadly prolong the expression of a pro-drug converting enzyme. Applicants also argued that TK in combination with GSV differs from P450 in combination with CPA because the active metabolites formed by TK and GSV are phosphorylated nucleosides that remain trapped within the tumor cell as they are generated and very little formation of soluble, diffusible metabolites. Additionally, overexpression of bcl-2 in HSVtk cells did not result in increased active, diffusible bystander cell-killing metabolites, but rather the GCV treatment of HSVtk cells expressing bcl-2 still led to eradication of the tumor cell population within a similar period of time.

Firstly, it appears that Applicants considered the teachings of the Melcher reference in total isolation from other cited references in the above 103(a) rejection, particularly the teachings of Waxman et al and Bilboa et al. It should be noted that since the above rejection was made under 35 U.S.C. 103(a), none of the cited references has to teach every limitation of the instant claims.

Secondly, contrary to Applicant's argument that dual-transduced HSVtk/bcl-2 cells do not die through apoptosis when exposed to GCV, Melcher et al stated clearly that "A population of CMT93tk cells, **in which a proportion of cells express bcl-2 by FACS, are still sensitive to GCV in vitro** but show greatly reduced amounts of

apoptotic cell death as judged by DNA ladders and propidium iodide staining". Moreover, Melcher et al also proposed **that necrotic cell death (another cell death mechanism) in vivo may provide a potent immunostimulatory signal that serves as a "danger" to allow breaking of tolerance to tumor antigens as a result of co-transfecting tumor cells with a vector encoding bcl-2. There is no teaching or suggestion whatsoever by the Melcher reference that tumor cells must not be transduced with a vector encoding with Bcl-2 for killing tumor cells in either in vitro or/and in vivo**. Please also note that the primary Waxman reference already taught explicitly methods of killing neoplastic cells using at least NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes (e.g., cyclophosphamide (CPA), ifosfamide (IFA) or any other P450-metabolized chemotherapeutic drug); and the P450/RED gene therapy approach may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines such as IL-2, IL-4 and IL-12; as well as with other established gene/produrg activation systems such as ganciclovir/HSV-TK.. Furthermore, Waxman et al also recognized that **current gene therapy technologies are limited by their inability to deliver prodrug activation or other therapeutic genes to a population of tumor cells with 100% efficiency but the effectiveness of this cancer gene therapy approach can be greatly enhanced by using with drugs exhibiting a strong bystander effect with bystander cytotoxicity resulting when**

active drug metabolites diffuse or otherwise transferred from their site of generation within a transduced tumor cell to a neighboring, naïve tumor cell leads to significant tumor regression even when a minority of tumor cell is tranduced with the prodrug activation gene.

Thirdly, Bilbao et al already demonstrated successfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically that "Strategies to prolong the expression of transgenes delivered by adenovirus vector, **even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical uti**lity". Furthermore, Waxman et al already disclosed that **some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression.** Accordingly, there is no surprise in adding an apoptosis inhibiting agent to a tumor cell **to prolong the expression of a pro-drug converting enzyme (e.g., P450/RED combination system) to enhance therapeutic effects via increased RED expression in tumor cells and/or to prolong production and secretion of cytotoxic drug metabolites in transduced tumor cells to neighboring native tumor cells to attain a prolonged bystander cytotoxicity that is known to lead to significant tumor regression** in light of the combined teachings of Waxman et al, Bilbao et al., Bullock et al, Melcher et al. and Beidler et al as set forth above.

2. With respect to the Bullock reference, Applicants pointed out that 4-hydroperoxyclophosphamide (4-HC) is a chemically-activated derivative of CPA, and not P450-activated CPA and 4-HC differs from P450-activated CPA in an important respect that 4-HC contributes substantially to apoptotic tumor cell death by stimulating the production of reactive oxygen species which are not formed when CPA is activated by P450 and thus the studies reported by Bullock were carried out on a drug that is fundamentally different from P450-activated CPA. Additionally, 4-HC and P450-activated CPA are fundamentally different in terms of the doses required because the 0.2 mM concentration of 4-HC used in Bullock is exceedingly high, supra-pharmacological concentration that can not be achieved in vivo or in cancer patients using CPA and are therefore not relevant. Furthermore, Bullock teaches decreasing the expression of bcl-2 facilitates 4HC-induced apoptosis which is the direct opposite of the present invention whereby the expression of the apoptotic inhibiting agent in the neoplastic cells blocks drug-induced apoptosis of that cell; and the reference fails to teach or suggest any method to promote expression of bcl-2 or any other anti-apoptotic gene expression in 4-HC treated cells or to promote the survival of human leukemia HL60 cells by increasing the expression of bcl-2 or by any other apoptosis inhibiting agent. With respect to the Bilbao reference, Applicants argued that Bilbao only teaches co-expression of bcl-2 gene to prolong the transgene expression within the same cell, but fails to teach or discuss any methods to increase expression of a prodrug converting enzyme or to teach or discuss use of any other apoptosis inhibiting agent to prolong survival of a neoplastic cell expressing a prodrug converting enzyme. With respect to

the Beidler reference, Applicants argue that the reference does not overcome the deficiency of Waxman, Bilbao, Bullock and Melcher because Beidler fails to suggest or teach expression of p35 in a cell expressing a prodrug converting enzyme or expression of p35 to prolong the lifespan of a tumor cell in order to increase the expression of a prodrug converting enzyme or expression of p35 to facilitate in the long term killing of tumor cells.

Firstly, the examiner would like to thank Applicants for pointing out that Bullock et al only teach that 4-HC is an active derivative of cyclophosphamide and not P450-activated CPA as stated by the Examiner in the previous office action. As explained by Applicants that 4-HC is decomposed in aqueous medium to yield 4OH-CPA plus hydrogen peroxide, while P450 activates CPA to form the same 4OH-CPA metabolite without the generation of hydrogen peroxide and reactive oxygen radicals. Nevertheless, the citation of the Bullock et al demonstrated that at the effective filing date of the present application **an active derivative of CPA** with or without cytokines (IL-3 and IL-6) was already shown to induce apoptosis in human myeloid leukemia cells and there is an inverse relationship between the level of bcl-2 and the level of induced apoptosis in the leukemia cells. **There is no evidence in either the Bullock reference or in the present application that the 4OH-CPA metabolite whether it is generated from 4-HC or P450-activated CPA would not be responsible for the observed induced apoptosis in cancer cells**. Upon reading the Bullock reference, an ordinary skilled artisan would concludes fairly that the metabolites of 4-HC, including 4OH-CPA, are responsible for the induced apoptosis in leukemia cells. With respect to

Applicants' other arguments on the Bullock reference, once again it appears that Applicants focused solely on the teachings of the Bullock reference without taking into consideration of the primary teachings of Waxman et al along with those of Bilbao et al and Melcher et al. Please note that **Waxman et al explicitly teach using anti-cancer drugs that are activated by P450 enzymes such as cyclophosphamide (CPA) and ifosfamide (IFA)**.

Secondly, with respect to Applicants' arguments on the Bilbao and Beidler references, it is noted again that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. It appears that Applicants argue each cited references individually, and without taking into consideration of the overall teachings of Waxman et al., Bilbao et al., Bullock et al, Melcher et al. and Beidler et al along with the stated motivations as set forth in the above 103(a) rejection.

Amended claims 14-18 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382), Bullock et al. (Exp. Hematol. 21:1640-1647, 1993), Melcher et al. (British Journal of Cancer 78:144-145, 1998) and Beidler et al. (J. Biol. Chem. 270:16526-16528, 1995) as applied to claims 1, 3, 8-11, 13 and 37-38 above, and further in view of Robertson et al (US 6,709,866) and Griffith et al. (US 6,900,185). ***This is a modified rejection necessitated by Applicant's amendment.***

The combined teachings of Waxman et al, Bilbao et al, Bullock et al, Melcher et al and Beidler et al. were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding the recited apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis, particularly p53 (elected species) expressed under control of a regulatable promoter, even though Waxman et al teach specifically that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines.

However, at the effective filing date of the present application Robertson et al already taught at least the use of a recombinant viral vector expressing various anti-apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient (see at least Summary of the Invention, particularly col. 3, lines 19-23; and cols. 20-22).

Additionally, Griffith et al already taught a method of inducing tumor cell apoptosis using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents or immune potentiating genes or proteins (see at least Summary of the Invention). Griffith et al further taught that Trail has an apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells (col. 1, lines 15-20). Griffith et al also disclosed

that expression of Trail/Apo2-L gene is under the control of a promoter, including an inducible promoter or a tissue-specific promoter (col. 10, lines 1-16).

It would have been obvious for an ordinary skilled artisan to further modify the teachings of Waxman et al, Bilbao et al, Bullock et al. Melcher et al. and Beidler et al., by also using a vector comprising a nucleic acid encoding the recited apoptosis inhibiting agent such as the baculovirus p35 protein (elected species) operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter in light of the teachings of Robertson et al. and Griffith et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because the expression of an antiapoptotic gene and/or an apopotic gene under a regulatable promoter *in vivo* has been widely used and applied in various gene therapy applications as taught by Robertson et al. and Griffith et al. Additionally, the expression of a transgene under a regulatable promoter can be turned on or off as needed or required by the treated patients. Furthermore, an ordinary skilled artisan would also have been motivated to select Trail/Apo2-L gene transfer to treat a mammal having a cancer due to its apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Bullock et al., Melcher et al.,

Beidler et al, Robertson et al.; Griffith et al., and coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 7/23/09 (pages 12-14) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the Robertson and Griffith references do not overcome the deficiency of Waxman, Bilbao, Bullock and Melcher for the reasons already stated in Applicants' responses for the rejection of claims 1, 3, 8-11, 13 and 37-38 above. Additionally, Applicants argued that the anti-apoptotic polypeptides in the Robertson reference were used for a completely different purpose, namely the anti-apoptotic polypeptides were expressed specifically to promote survival of a neuron cell; and under no circumstances would it be obvious to use anti-apoptotic polypeptides to prevent the loss of tumor cells.

Firstly, please refer to the examiner's responses to Applicants' arguments for the rejection of claims 1, 3, 8-11, 13 and 37-38 above.

Secondly, the teachings of Robertson et al should be read in light of the combined teachings of Waxman, Bilbao, Bullock, Melcher and Beidler as set forth

above and not in total isolation. The citation of the Robertson reference is mainly for the use of regulatable promoters to control the expression of anti-apoptotic genes.

Thirdly, at least Melcher et al already taught transfecting tumor cells with a vector encoding bcl-2, an anti-apoptotic agent, in vitro and/or in vivo. Additionally, please note that the expression of an anti-apoptotic agent in tumor cells can be made transiently or controlled via the use of replicative-defective adenovirus vector and/or regulatable promoters.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633